

Title 8, CALIFORNIA CODE OF REGULATIONS, SECTION 9792.20 ET AL.  
INITIAL STATEMENT OF REASONS  
APPENDIX B—CHRONIC PAIN MEDICAL TREATMENT GUIDELINES (DWC 2008)  
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Labor Code section 5307.27 requires the Administrative Director to adopt a medical treatment utilization schedule (MTUS) that is “scientific and evidence-based, peer-reviewed, and nationally recognized.” (See, also Lab. Code, § 4604.5(b).) Labor Code section 4604.5(e) and California Code of Regulations, title 8, section 9792.22(b) [now proposed Section 9792.25(b)] provide that for all injuries not addressed by the MTUS, treatment shall be authorized in accordance with other nationally recognized medical treatment guidelines that are “scientifically and evidence-based.” Labor Code section 5307.27 further provides that the MTUS shall address, at a minimum, “the frequency, duration, intensity, and appropriateness of all treatment procedures and modalities commonly performed in workers’ compensation cases.”

The Chronic Pain Medical Treatment Guidelines (DWC 2008) replaces the ACOEM’s Practice Guidelines’ Chapter 6—*Pain, Suffering, and the Restoration of Function* (Chapter 6) relating to chronic pain, which was originally adopted as part of the MTUS, effective June 15, 2007. The chronic pain medical treatment guidelines are being adapted from the Work Loss Data Institute’s Official Disability Guidelines (ODG) Treatment in Workers’ Comp – Chapter on Pain (Chronic). The version being adapted is dated October 31, 2007. The 2005 RAND Report identified the ODG Guidelines as meeting the requirements of Labor Code section 5307.27. (2005 RAND Report, Table 4, p. 21; Table 4.2, p. 27.) Based on RAND’s findings, the Administrative Director determined it appropriate to adapt the chronic pain medical treatment guidelines from the ODG chapter on pain.

The medical evidence evaluation advisory committee (MEEAC), as created by California Code of Regulations, title 8, section 9792.23(a) (8 CCR 9792.23(a)) [now proposed Section 9792.26(a)], has reviewed the ODG chapter on pain and the evidence for purposes of supplementing the MTUS in the identified high priority area of chronic pain. (2005 RAND Report, at pp. 56, 85, and 86.) The following delineates MEEAC’s participation in advising the Administrative Director via the Medical Director and the Medical Unit’s research staff regarding the proposed chronic pain medical treatment guidelines.

In evaluating evidence when making recommendations to revise, update or supplement the MTUS, the MEEAC is required pursuant to 8 CCR 9792.23(c)(1)-(c)(3) [now proposed Section 9792.26(c)(1)-(c)(3)], to:

- (1) Apply the requirements of subdivision (b) of Section 9792.22 in reviewing medical treatment guidelines to insure that the guidelines are scientifically and evidence-based, and nationally recognized by the medical community;
- (2) Apply the ACOEM’s strength of evidence rating methodology to the scientific evidence as set forth in subdivision (c) of Section 9792.22 after identifying areas in the guidelines which do not meet the requirements set forth in subdivision (b) of Section 9792.22;

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(3) Apply in reviewing the scientific evidence, the ACOEM's strength of evidence rating methodology for treatments where there are no medical treatment guidelines or where a guideline is developed by the Administrative Director, as set forth in subdivision (c) of Section 9792.22.

Because the 2005 RAND Report identified the ODG Guidelines as meeting the requirements of Labor Code section 5307.27, DWC determined that it was not necessary to require the MEEAC to review the ODG chapter on pain to determine whether the guideline was "nationally recognized" and "scientifically and evidence-based." (8 CCR 9792.23(c)(1) [now proposed Section 9792.26(c)(1)].) For the same reason, DWC determined that it was not necessary to require the MEEAC to review the ODG chapter on pain to identify areas which are not "scientifically and evidence-based." (8 CCR 9792.23(c)(2) [now proposed Section 9792.26(c)(2)].) However, because the chronic pain medical treatment guidelines is an adaptation of the ODG chapter on pain, the MEEAC reviewed the ODG chapter on pain and applied the requirements of 8 CCR 9792.23(c)(3) [now proposed Section 9792.26(c)(3)].

In applying the requirements of this section, MEEAC reviewed the ODG chapter on pain to identify individual treatment topics which were not addressed in the ODG chapter on pain. The chronic pain treatment guidelines were supplemented by adding the identified individual treatment topics to the guidelines. In supplementing the chronic pain medical treatment guidelines, the MEEAC applied the ACOEM's strength of evidence rating methodology set forth in 8 CCR 9792.22(c) [now proposed Section 9792.25(c)] pursuant to 8 CCR 9792.23(c)(3) [now proposed Section 9792.26(c)(3)]. The MEEAC via the medical unit's research staff conducted evidence-based reviews (EBRs) by conducting a literature search on PubMed after formulating appropriate search terms. Upon conducting the literature search, relevant articles were selected. The selection of the articles was conducted applying ACOEM's *Methodology for the Update of the Occupational Medicine Practice Guidelines, 2<sup>nd</sup> Edition* "Table A: Criteria for Accepting Studies as Containing Adequate Evidence (Article Inclusion Criteria)" (At p. 18.) The selected articles were graded according to the strength of evidence rating methodology set forth in 8 CCR 9792.22(c) [now proposed Section 9792.25(c)], and recommendations for individual treatment topics were developed.

Further, in making recommendations to the Administrative Director via the Medical Director to supplement the MTUS, the MEEAC is responsible to evaluate the developed guidelines to insure that the guidelines conform to the framework of the MTUS. The MEEAC must further take into consideration Labor Code section 4604.5(a), which provides that the MTUS is presumed to be "correct on the issue of extent and scope of medical treatment" provided to injured employees. Clarity in the guidance of the guidelines facilitates appropriate treatment which is presumed to be correct pursuant to the Labor Code and avoids delayed treatment, thus encouraging prompt recovery and reduced disability.

The MEEAC evaluated the ODG chapter on pain to determine that the individual treatment topics contained in the chapter conformed to the framework of the MTUS. One of the areas

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identified which did not conform to the framework of the MTUS is the use of the term “under study.” The term “under study” indicates that the evidence was reviewed but ODG was unable to make a recommendation either in support or against the treatment based on the insufficiency of the evidence. Because the MTUS is presumed to be correct on the issue of extent and scope of medical treatment and because of the lack of guidance in the ODG chapter on pain on these topics, it was necessary for the DWC to conduct EBRs on these individual treatment topics to determine whether or not the treatment should be recommended. Just because the evidence is not sufficient, this does not necessarily mean that the individual treatment topic should not have a recommendation.

Another area identified by the MEEAC which does not conform to the framework of the MTUS is the herbal therapies and nutritional supplements. Herbal therapies and nutritional supplements are not considered drugs by the FDA, rather they are considered foods or dietary supplements.

Labor Code section 5307.27 requires the Administrative Director to adopt an MTUS that incorporates evidence-based, peer-reviewed, nationally recognized standards of care, and that addresses the frequency, duration, intensity, and appropriateness of all treatment procedures and modalities commonly performed in workers' compensation cases. The Federal Drugs Administration (FDA) does not regulate the manufacturing of foods or dietary supplements listed above:

Currently, there are no FDA regulations that are specific to dietary supplements that establish a minimum standard of practice for manufacturing dietary supplements. However, [the] FDA intends to issue regulations on good manufacturing practices that will focus on practices that ensure the identity, purity, quality, strength and composition of dietary supplements. At present, the manufacturer is responsible for establishing its own manufacturing practice guidelines to ensure that the dietary supplements it produces are safe and contain the ingredients listed on the label. See U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, January 3, 2001, Overview of Dietary Supplements.(<http://vm.cfsan.fda.gov/~dms/ds-overview.html>.)

Thus, recommending these individual treatment topics would not conform to the requirements of the Labor Code section 5207.27 requiring that the MTUS address the “intensity” of treatment. The MTUS will be revised when the FDA issue regulations on good manufacturing practices that will focus on practices that ensure the identity, purity, quality, strength and composition of dietary supplements.

The following list represents the format of the EBRs conducted: (1) Topic Heading, (2) Treatment Guideline, (3) Date of review, (4) Treatment recommendation, (5) Background research, (6) Search criteria (7) Search terms, (8) Findings, (9) Strength of evidence, (10) MEEAC Comments (if any), (11) Evidence lists.

## **Individual Medical Treatment Guidelines**

### **Clonidine, Intrathecal**

Recommended. The evidence supports the use of intrathecal clonidine alone or in conjunction with opioids (e.g., morphine) and local anesthetics (e.g., bupivacaine) in the treatment of Complex Regional Pain Syndrome/Reflex Sympathetic Dystrophy (CRPS/RSD). Intrathecal clonidine can also be used in conjunction with opioids for neuropathic pain. There is no evidence that intrathecal clonidine alone is effective in the treatment of pain after spinal cord surgery. There are no studies that address the use of intrathecal clonidine beyond 18 months.

**Date of Review: March 3, 2008**

**ODG States:** Understudy. There is little evidence that this medication provides long-term pain relief (when used in combination with opioids approximately 80% of patients had < 24 months of pain relief) and no studies have investigated the neuromuscular, vascular or cardiovascular physiologic changes that can occur over long period of administration. Side effects include hypotension, and the medication should not be stopped abruptly due to the risk of rebound hypertension. The medication is FDA approved with an orphan drug intrathecal indication for cancer pain only. Clonidine is thought to act synergistically with opioids. Most studies on the use of this drug intrathecally for chronic non-malignant pain are limited to case reports. ([Ackerman, 2003](#)) Clonidine (Catapres) is a direct-acting adrenergic agonist prescribed historically as an antihypertensive agent, but it has found new uses, including treatment of some types of neuropathic pain.

**Search Criteria:** Performed a Medline/PubMed search for randomized controlled trials that examined the efficacy of Clonidine, intrathecal in the treatment of chronic pain.

#### **Search Terms:**

Clonidine  
Clonidine and Chronic Pain  
Clonidine and Pain  
Intrathecal Clonidine  
Intrathecal Clonidine and Chronic Pain  
Intrathecal Clonidine and Pain

**Findings:** One intermediate quality randomized controlled trial found that intrathecal clonidine alone worked no better than placebo. It also found that clonidine with morphine worked better than placebo or morphine or clonidine alone.

**Strength of Evidence: C**

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**Evidence:**

Siddall, P., et al. The efficacy of Intrathecal Morphine and Clonidine in the Treatment of Pain After Spinal Cord Injury. *Anesh. Analg*, 2000; Number 91:1493-8. **Quality:** Intermediate **Total Rating:** 7.5 **Comment:** 15 patients were divided into research groups. Found that intrathecal clonidine alone did not perform better than placebo.

Hassenbusch, S. Intrathecal Clonidine in the Treatment of Intractable Pain: A Phase I/II Study” *Pain Medicine*. 2002; Volume 3, Number 2: 85-91. **Quality:** Low **Total Rating:** 2.0 **Comment:** Does not meet inclusion criteria for evidence-based review.

Raphael, J., et al. Long-term experience with implanted intrathecal drug administration systems for failed back syndrome and chronic mechanical low back pain. *BMC Musculoskeletal Disorders*. 2002; Volume 3, Number 17. **Quality:** Low **Total Rating:** 2.0 **Comment:** Does not meet inclusion criteria for evidence-based review.

Ackermann, L., Follett, K., Rosenquist, R. “Long-Term Outcomes During Treatment of Chronic Pain with Intrathecal Clonidine or Clonidine/Opioid Combinations” *Journal of Pain and Symptom Management*. 2003; July, Volume 26: 668-76. **Quality:** Low **Total Rating:** 1.0 **Comment:** Does not meet inclusion criteria for evidence-based review.

Martin, T., et al. Pharmacology of Opioid and Nonopioid Analgesics in Chronic Pain. *The Journal of Pharmacology and Experimental Therapeutics*. 2001; Volume 299, Number 3: 811-7. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Roberts, L. J., et al. Outcome of intrathecal opioids in chronic non-cancer pain *European Journal of Pain*. 2001; Number 5: 353-361. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Taricco, M., et al. Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review. *Eura Medicophys*. 2006; Volume 42: 5-15. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

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**Cytokine DNA Testing**

Not recommended. There is no current evidence to support the use of cytokine DNA testing for the diagnosis of pain, including chronic pain. Scientific research on cytokines is rapidly evolving.

**Date of Last Review: December 10, 2007**

**Reason for evidence review:** There is vast and growing scientific evidence base concerning the biochemistry of inflammation and it is commonly understood that inflammation plays a key role in injuries and chronic pain. Cellular mechanisms are ultimately involved in the inflammatory process and healing, and the molecular machinery involves cellular signaling proteins or agents called cytokines. Given rapid developments in cytokine research, novel applications have emerged and one application is cytokine DNA signature testing which has been used as a specific test for certain pain diagnoses such as fibromyalgia or complex regional pain syndrome. An EBR was conducted to review the scientific evidence base for cytokine DNA testing for pain.

**Background Research:** DWC determined that the specific test for cytokine DNA testing is performed by the Cytokine Institute ([www.cytokineinstitute.com](http://www.cytokineinstitute.com)). In further review of their website, we found specific research articles cited in support of cytokine DNA testing.

**Findings:** Two articles were found on the website. However, these articles did not meet the minimum standards for inclusion for evidence-based review.

**Strength of Evidence: I**

**Evidence:**

Gavin, I., et al. Identification of Human Cell Responses to Hexavalent Chromium *Environmental and Molecular Mutagenesis*. 2007. Volume 48: 650-57.. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Gillis, B., et al. Identification of Human cell responses to benzene and benzene metabolites" *Genomics*. 2007; Number 90: 324-33. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

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**Functional MRI**

Not recommended. Functional neuroimaging is helping to identify the sensory and emotional components of pain and its autonomic responses, and may help in the design of more rational treatments for pain. However, this test is only useful in a research setting at this time and does not have a role in the evaluation or treatment of patients.

**Date of Review: December 12, 2007**

**Search Criteria:** Performed a Medline/PubMed search for randomized controlled trials that examined the efficacy of functional MRI in the treatment of chronic pain.

**Search Terms:**

Functional MRI

Functional MRI and Chronic Pain

**Findings:** There are no studies about the use of functional MRI in a clinical setting.

**Strength of Evidence:** I

**Evidence:**

Borsook, D., et al. Neuroimaging revolutionizes therapeutic approaches to chronic pain. *Molecular Pain*. 2000; Volume 3, Number 25. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

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**Intravenous Regional Sympathetic Blocks (for RSD, nerve blocks)**

Not recommended. However, if other treatments are contraindicated (e.g. when a stellate ganglion block cannot be done due to bleeding diathesis) intravenous regional blocks may be performed. IV regional blocks, also known as Bier blocks, are not commonly done for RSD. Although there is no scientific evidence to support this treatment, it is recommended as an option in certain cases when there are no other alternatives. When the procedure is performed, it must be done in conjunction with a rehabilitation program. There is no role for intravenous regional sympathetic blocks for the diagnosis of RSD.

**Date of Review: December 17, 2007**

**Search Criteria:** Performed a Medline/PubMed search for randomized controlled trials that examined the efficacy of intravenous regional sympathetic blocks and RSD blocks in the treatment of chronic pain.

**Search Terms:**

Intravenous Regional Sympathetic Blocks  
Intravenous Regional Sympathetic Blocks and Chronic Pain  
RSD and Chronic Pain

**Findings:** The search found one intermediate trial suggesting benefit from intravenous regional sympathetic blocks.

**Strength of Evidence: C**

**Evidence:**

Ramamurthy S, et al. Intravenous Regional Guanethidine in the Treatment of Reflex Sympathetic Dystrophy/Causalgia: A Randomized, Double-Blind Study. *Anesth Analg*. 1995; Volume 81:718-23.

**Quality:** Intermediate **Total Rating:** 8 **Comment:** Found that guanethidine was no better than the placebo in improving pain scores for patients with RSD.

Jadad, A., et al. Intravenous Regional Sympathetic Blockade for Pain Relief in Reflex Sympathetic Dystrophy: A Systematic Review and a Randomized, Double-Blind Crossover Study. *Journal of Pain Symptom Management*. 1995; Volume 10:13-20. **Quality:** N/A **Total Rating:** N/A **Comment:** Meta-Analysis Does not meet inclusion criteria for evidence-based review.

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**Ketamine**

Not recommended. There is insufficient evidence to support the use of ketamine for the treatment of chronic pain.

**Date of Review: December 18, 2007**

**Search Criteria:** Performed a Medline/PubMed search for randomized controlled trials that examined the efficacy of ketamine in the treatment of chronic pain

**Search Terms:**

Ketamine

Ketamine and Pain

Ketamine and Chronic Pain

**Findings:** There are no quality studies that support the use of ketamine for chronic pain.

**Strength of Evidence:** I

**Evidence:**

Rabben, T. Prolonged Analgesic Effect of Ketamine, a N-Methyl-D-Aspartate Receptor Inhibitor, in Patients with Chronic Pain. *The Journal of Pharmacology and Experimental Therapeutics*. 1999; Volume 289:1060-66. **Quality:** Low **Total Rating:** 3.0 **Comment:** Does not meet inclusion criteria for evidence-based review.

Correll, G., et al. Subanesthetic Ketamine Infusion Therapy: A Retrospective Analysis of a Novel Therapeutic Approach to Complex Regional Pain Syndrome. *Pain Medicine* 2004; Volume 5, Number 3: 263-75. **Quality:** Low **Total Rating:** 2.5 **Comment:** Does not meet inclusion criteria for evidence-based review.

Grant, I. S., et al. Pharmacokinetics and Analgesic Effects of I.M. and Oral Ketamine. *British Journal Anesthesiology*. 1981; Volume 53, 805-10. **Quality:** Low **Total Rating:** 2.5 **Comment:** Does not meet inclusion criteria for evidence-based review.

Goldberg, M., et al. Multi-Day Low Dose Ketamine Infusion for the Treatment of Complex Regional Pain Syndrome. *Pain Physician*. 2005; Volume 8, Number 2: 175-19. **Quality:** Low **Total Rating:** 1.0 **Comment:** Does not meet inclusion criteria for evidence-based review.

Hocking, G., et al. Ketamine in Chronic Pain Management. *Anesth. Analg*, 2003; Volume 97: 1730-9. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Reuben, S. and Buvandendran A. Preventing the Development of Chronic Pain after Orthopedic Surgery with Preventive Multimodal Analgesic Techniques. *Journal of Bone and Joint Surgery*. 2007. Volume

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89: 1343-58. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Visser, E. and Shurg, S. A. "The role of ketamine in pain management" *Biomedicine and Pharmacotherapy* 2006; Volume 60: 341-348. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Wood, P. A Reconsideration of the Relevance of Systemic Low-Dose Ketamine to the Pathophysiology of Fibromyalgia. *The Journal of Pain*. 2006 Volume 7, Number 9: 611-14. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

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**Neuromuscular electrical stimulation (NMES devices)**

Not recommended. NMES is used primarily as part of a rehabilitation program following stroke and there is no evidence to support its use in chronic pain.

**Date of Review: December 17, 2007**

**Search Criteria:** Performed a Medline/PubMed search for randomized controlled trials that examined the efficacy of NMES in the treatment of chronic pain.

**Keywords:**

Neuromuscular electrical stimulation  
Neuromuscular electrical stimulation and Pain  
Neuromuscular electrical stimulation and Chronic Pain  
NMES  
NMES and Pain  
NMES and Chronic Pain

**Findings:** The above-described search found no intervention trials suggesting benefit from NMES for chronic pain.

**Strength of Evidence:** (I)

**Evidence:**

Moore, S and Shurman J. Combined Neuromuscular Electrical Stimulation and Transcutaneous Electrical Nerve Stimulation for Treatment of Chronic Back Pain: A Double-Blind, Repeated Measures Comparison. *Archive of Physical Medicine and Rehabilitation*. 1997; Volume 78, January: 55-60.  
**Quality:** Low **Total Rating:** 3.5 **Comment:** Does not meet inclusion criteria for evidence-based review.

Gaines, J., et al. The Effect of Neuromuscular Electrical Stimulation on Arthritis Knee Pain in Older Adults with Osteoarthritis of the Knee *Applied Nursing Research* 2004. August; Volume 17, Number 3: 201-06. **Quality:** Low **Total Rating:** 3.0 **Comment:** Does not meet inclusion criteria for evidence-based review.

Renzenbrink, G. and Ijzerman M. Percutaneous neuromuscular electrical stimulation (P-NMES) for treating shoulder pain in chronic hemiplegia. Effects on Shoulder pain and quality of life. *Clinical Rehabilitation*. 2004; Volume 18:359-653. **Quality:** N/A **Total Rating:** N/A **Comment:** article excluded because it is percutaneous and the study is on stroke patients

Sheffler, L. and J. Chae. Neuromuscular Electrical Stimulation in Neurorehabilitation. *Muscle Nerve* Volume 2007; 35: 562-90. **Quality:** N/A **Total Rating:** N/A **Comment:** Article excluded because of stroke or spinal cord injury

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Van Til, J., et al. A preliminary economic evaluation of percutaneous neuromuscular electrical stimulation in the treatment of hemiplegic shoulder pain. *Disability and Rehabilitation*. 2006; Volume 28, Number 10:645-51. **Quality:** N/A **Total Rating:** N/A **Comment:** article excluded because it is percutaneous and the study is on stroke patients

Yu, D., et al. Intramuscular Neuromuscular Electrical Stimulation for Poststroke Shoulder Pain: A Multicenter Randomized Clinical Trial. *Archive of Physical Medicine and Rehabilitation*. 2004; Volume 85, May: 695-704 **Quality:** N/A **Total Rating:** N/A **Comment:** article excluded because it is percutaneous and the study is on stroke patients

Zorn, C., et al. Effects of neuromuscular electrical stimulation of the knee extensor muscles on muscle soreness and different serum parameters in young male athletes: preliminary data. *British Journal of Sports Medicine*. 2007; Volume 41: 914-6 **Quality:** N/A **Total Rating:** N/A **Comment:** article excluded because it is not a pain study.

### **Testosterone Replacement for Hypogonadism**

Recommended in limited circumstances for patients taking high-dose long-term opioids with documented low testosterone levels. Hypogonadism has been noted in patients receiving intrathecal opioids and long term high dose opioids. Routine testing of testosterone levels in men taking opioids is not recommended. However, an endocrine evaluation and/or testosterone levels should be considered in men who are taking long term, high dose oral opioids or intrathecal opioids and who exhibit symptoms or signs of hypogonadism, such as gynecomastia. If needed, testosterone replacement should be done by a physician with special knowledge in this field given the potential side effects such as hepatomas. There are multiple delivery mechanisms for testosterone Hypogonadism secondary to opiates appears to be central, although the exact mechanism has not been determined.

**Date of Review: December 20, 2007**

**Background Research:** ODG's section states:

#### **Testosterone replacement for hypogonadism (related to opioids) [ODG]**

Under study. Hypogonadism has been noted in patients receiving intrathecal opioids. This appears to be more pronounced than in patients taking oral opiates and this difference seems to be related to differences in absorption. Hypogonadism secondary to opiates appears to be central, although the exact mechanism has not been determined. (Abs, 2000) (Roberts, 2002) (Roberts, 2000) Etiology of decreased sexual function, a symptom of hypogonadism, is confounded by several factors including the following: (1) The role of chronic pain itself on sexual function; (2) The natural occurrence of decreased testosterone that occurs with aging; (3) The documented side effect of decreased sexual function that is common with other medications used to treat pain (SSRIs, tricyclic antidepressants, and certain anti-epilepsy drugs); & (4) The role of comorbid conditions such as diabetes, hypertension, and vascular disease in erectile dysfunction. There is little information in peer-reviewed literature as to how to treat opioid induced androgen deficiency.

Long-term safety data of testosterone replacement (overall): Not available.

Cardiovascular risk: There have been no large randomized controlled trials to evaluate the cardiovascular risk associated with long-term testosterone use, although current studies weakly support that there is no association with important cardiovascular effects. (Haddad 2007)

Osteoporosis: The extent to which testosterone can prevent and treat osteoporosis remains unclear. (Tracz 2006) (Isidori, 2005)

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Sexual function: Current trials of testosterone replacement in patients with documented low testosterone levels have shown a moderate nonsignificant and inconsistent effect of testosterone on erectile function, a large effect on libido, and no significant effect on overall sexual satisfaction. (Bolona, 2007) (Isidori, 2005)

The one study (sponsored by the drug company) that has evaluated the use of testosterone replacement in patients with opioid-induced androgen deficiency, measured morning serum free testosterone levels and PSA prior to replacement. This study did not include patients taking antidepressants. (Daniell, 2006)

**Search Criteria:** Performed a Medline/PubMed search for randomized controlled trials that examined the link between Hypogonadism and testosterone replacement

**Search Terms:**

Opioids and testosterone

Hypogonadism and testosterone replacement

**Findings:** The evidence on testosterone levels in long-term opioid users is not randomized or double-blinded. However, there are studies that show that there is an increased incidence of hypogonadism in people taking opioids, either intrathecal or oral. There is also a body of literature showing that improvement in strength and other function in those who are testosterone deficient who receive replacement.

**Strength of Evidence:** C, supporting testosterone replacement for hypogonadism. C, supporting the correlation between hypogonadism and opioid use.

**Evidence:**

Page, S., et al. (2005) "Exogenous Testosterone (T) alone or with Finasteride Increases Physical Performance, Grip Strength, and Lean Body Mass in Older Men with Low Serum T" *Journal of Clinical Endocrinology & Metabolism*, Volume 90, Number 3, 1502-1510. **Quality:** Intermediate **Total Rating:** 7.0 **Comment:** Study looks at an older population of men than typically represented in the Work Comp setting 70+. Has a high drop-out rate. However, it does score high in areas of randomization and blinding. In the end it finds that Exogenous Testosterone therapy and Exogenous Testosterone therapy with Finasteride Increases Physical Performance can increase physical function in older men with low levels of serum Testosterone.

Abs, R., et al. Endocrine Consequences of Long-Term Intrathecal Administration of Opioids. *The Journal of Clinical Endocrinology & Metabolism*. 2000; Volume 85, Number 6: 2215-22. **Quality:** Low **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Wang, C., et al. New Testosterone Buccal System (Striant) Delivers Physiological Testosterone Levels: Pharmacokinetics Study in Hypogonadal Men. *The Journal of Clinical Endocrinology & Metabolism*.

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2004; Volume 89, Number 8, 381-29. **Quality:** Low **Total Rating:** 3.0 **Comment:** Does not meet inclusion criteria for evidence-based review.

Rajagopal, A., et al. Symptomatic Hypogonadism in Male Survivors of Cancer with Chronic Exposure to Opioids" *Cancer*. 2004; Volume 100, Number 4, 851-858. **Quality:** Low **Total Rating:** 1.5 **Comment:** Does not meet inclusion criteria for evidence-based review.

Nakazawa, R., et al. Hormone Profiles after Intramuscular Injection of Testosterone Enanthate in Patients with Hypogonadism. *Endocrine Journal*, 2006; Volume 53, Number 3, 305-103. **Quality:** Low **Total Rating:** .5 **Comment:** Does not meet inclusion criteria for evidence-based review.

Carnegie, C., et al. Diagnosis of Hypogonadism: Clinical Assessments and Laboratory Tests. *Rev Urol*. 2006; Volume 6, Supplement 6, S3-S8. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

Nieschlag, E., et al. Testosterone replacement therapy: current trends and future directions. *Human Reproduction Update*. 2004; Volume 10, Number 5, 409-19. **Quality:** N/A **Total Rating:** N/A **Comment:** Does not meet inclusion criteria for evidence-based review.

### **Topical Analgesics-Compounded**

Not recommended. There is mixed evidence about whether compounding topical medications, such as adding an anti-inflammatory agent to capsaicin, is more efficacious than the single medication. Furthermore, a recent FDA warning about the potential dangers of compounded topical medication containing local anesthetics supersedes any recommendation (U.S. Food and Drug Administration, FDA News, December 5, 2006, FDA Warns Five Firms to Stop Compounding Topical Anesthetic Creams. (<http://www.fda.gov/bbs/topics/NEWS/2006/NEW01516.html>)). The FDA warns, that exposure to high concentrations of local anesthetics, like those in compounded topical anesthetic creams, can cause grave reactions including seizures, irregular heartbeats and death.

**Date of Review: December 12, 2007**

**Reason for evidence review:** ODG has the following statement: “Many agents are compounded as monotherapy or in combination for pain control (including NSAIDs, opioids, capsaicin, local anesthetics, antidepressants, glutamate receptor antagonists,  $\alpha$ -adrenergic receptor agonist, adenosine, cannabinoids, cholinergic receptor agonists,  $\gamma$  agonists, prostanoids, bradykinin, adenosine triphosphate, biogenic amines, and nerve growth factor). ([Argoff, 2006](#)) There is little to no research to support the use of many these agents. The use of these compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required.”

**Search Criteria:** Performed a Medline/PubMed search for randomized controlled trials that examined the efficacy of compounded topical medications in the treatment of chronic pain

**Search Terms:**

Topical compounded medications

Topical medications and chronic pain

**Findings:** Five intermediate randomized controlled studies were found. One randomized controlled trial found that neither the use of Topical 2% Amitriptyline and Topical 1% Ketamine nor both in conjunction perform better than placebo. Another study by the same authors found the opposite. A third study found that compared topical doxepin, capsaicin and compounded doxepin/capsaicin to placebo, and all 3 treatments performed better than placebo, but the combination did not perform as well as the single agent. A fourth study, found in an unrepresentative sample of osteoarthritis patients that capsaicin and glyceryl trinitrate in combination may outperform placebo in treating osteoarthritis pain. A fifth study found that a reduction in pain intensity was observed with topical lidocaine; no significant change in pain intensity was found with topical amitriptyline or placebo; in pairwise comparison of treatments, topical lidocaine and placebo each reduced pain more than topical amitriptyline.

Title 8, CALIFORNIA CODE OF REGULATIONS, SECTION 9792.20 ET AL.  
INITIAL STATEMENT OF REASONS  
APPENDIX B—CHRONIC PAIN MEDICAL TREATMENT GUIDELINES (DWC 2008)  
EVIDENCE-BASED REVIEWS

**Strength of Evidence:** C, There is grade C evidence demonstrating that compounded topical analgesic agents are not more efficacious than commercially available single agents. There is also grade C evidence demonstrating that compounded topical analgesic agents are more efficacious.

**Evidence:**

McCleane, G. Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *British Journal Clinical Pharmacology*. 2000 June; Volume 49, Issue 6, Page 574-9. **Quality:** Intermediate **Total Rating:** 7 **Comment:** Authors conclusions not consistent with his data. The data shows that while the use of Doxepin and Capsaicin together provide analgesia, the use of the two in combination actually underperforms the use of Capsaicin alone.

Ho, Kok-Yuen, et al. Topical Amitriptyline Versus Lidocaine in the Treatment of Neuropathic Pain. *Clinical Journal of Pain*. 2008; Volume 24, Number 1, January: 51-55.. **Quality:** Intermediate **Total Rating:** 6.5 **Comment:** Authors found that a reduction in pain intensity was observed with topical lidocaine; no significant change in pain intensity was found with topical amitriptyline or placebo; in pairwise comparison of treatments, topical lidocaine and placebo each reduced pain more than topical amitriptyline.

Lynch, M., et al. Topical 2% Amitriptyline and 1% Ketamine in Neuropathic Pain Syndromes: A Randomized, Double-blind, Placebo-controlled Trial. *Anesthesiology*. 2005; Volume 103:140-6. **Quality:** Intermediate **Total Rating:** 6.0 **Comment:** Authors conclude that neither the use of Topical 2% Amitriptyline and Topical 1% Ketamine nor both in conjunction perform better than placebo.

McCleane, G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. *European Journal of Pain* 2000; Volume 4: 355-60. **Quality:** Intermediate **Total Rating:** 6.0 **Comment:** Study found that capsaicin and glyceryl trinitrate in combination outperformed placebo in treating osteoarthritis pain. Those on the combination were more willing to stay on the treatment. Study by its own admission did not use a representative sample of osteoarthritis patients.

Lynch, M., et al. Topical Amitriptyline and Ketamine in Neuropathic Pain Syndromes: An Open-Label Study. *The Clinical Journal of Pain*. 2005; Volume 6, Number 10, October: 644-49. **Quality:** Intermediate **Total Rating:** 4.5 **Comment:** Authors conclude that neither the use of Topical 2% Amitriptyline and Topical 1% Ketamine nor both in conjunction perform better than placebo. Authors add that the combination of Topical 2% Amitriptyline and Topical 1% Ketamine may provide long-term benefit to patients with neuropathic pain.

Lynch, M. et al. "A Pilot Study Examining Topical Amitriptyline, Ketamine, and a Combination of Both in the Treatment of Neuropathic Pain," *The Clinical Journal of Pain* Volume 2003 19: 323-8. **Quality:** Low **Total Rating:** 3.0 **Comment:** Does not meet inclusion criteria for evidence-based review.